Beta-Lactam Antibiotics & Other Cell Wall Synthesis Inhibitors

CEPHALOSPORINS

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins.

Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to *7-aminocephalosporanic acid*. Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms.

However, they tend to be more resistant than the penicillins to certain β-lactamases.

Pharmacokinetics

Several cephalosporins are available for oral use, but most are administered parenterally.

Cephalosporins with side chains may undergo hepatic metabolism, but the *major elimination mechanism* for drugs in this class is *renal excretion via active tubular secretion.*

Cefoperazone and ceftriaxone are excreted mainly in the bile.

Most *first- and second-generation cephalosporins* do *not enter the cerebrospinal fluid* even when the meninges are inflamed.

Mechanisms of Action and Resistance

Cephalosporins bind to PBPs on bacterial cell membranes to inhibit bacterial cell wall synthesis by mechanisms similar to those of the penicillins. *Cephalosporins are bactericidal* against susceptible

organisms.

Cephalosporins less susceptible to penicillinases produced by staphylococci, but many bacteria are resistant through the production of *other betalactamases* that can inactivate cephalosporins.

Resistance can also result from decreases in membrane permeability to cephalosporins and from changes in PBPs.

Methicillin-resistant staphylococci are also resistant to cephalosporins.

- **Clinical Uses**

1. **First-generation drugs—Cefazolin (parenteral) and cephalexin (oral) are examples of this subgroup.**

They are active against gram-positive cocci, including staphylococci and common streptococci. Many strains of *E coli* and *K pneumoniae* are also sensitive.

- **Clinical uses include treatment of infections caused by these organisms and surgical prophylaxis in selected conditions.**

2. Second-generation

have slightly less activity against gram-positive organisms than the first-generation drugs but *have an extended gram-negative coverage*.

Marked differences in activity occur among the drugs in this subgroup. Examples of clinical uses *include infections caused by the anaerobe Bacteroides fragilis* (cefotetan, cefoxitin) and sinus, ear, and respiratory infections caused by *H influenzae or M catarrhalis* (cefamandole, cefuroxime, cefaclor).

3. Third-generation drugs:

(eg, ceftazidime, cefoperazone, cefotaxime)

include increased activity against gram-negative organisms resistant to other beta-lactam drugs and ability to penetrate the blood-brain barrier (except cefoperazone and cefixime).

- **Most are active against *Providencia, Serratia marcescens*, and beta-lactamase producing**

strains of *H influenzae and Neisseria*

- **Ceftriaxone and cefotaxime are currently the**

most active cephalosporins against penicillin-resistant pneumococci (PRSP strains)

- **Also have activity against *Pseudomonas* (cefoperazone, ceftazidime) and *B fragilis* (ceftizoxime)**
- **Ceftriaxone (parenteral) and cefixime (oral), currently drugs of choice in gonorrhea.**

4. Fourth-generation drugs—

- **Cefepime** is more ***resistant to beta-lactamases*** produced by gram-negative organisms, including

Enterobacter, Haemophilus, Neisseria, and some ***penicillin resistant pneumococci***.

- **Cefepime** combines the gram-positive activity of first-generation agents with the wider gram-negative

spectrum of third-generation cephalosporins.

- **Ceftaroline** has activity in infections caused by methicillin-resistant staphylococci.

Toxicity

1. Allergy—Cephalosporins cause a range of allergic reactions from skin rashes to anaphylactic shock. These reactions occur *less frequently with cephalosporins than with penicillins*.

Complete cross-hypersensitivity between different cephalosporins should be assumed. Cross-reactivity between penicillins and cephalosporins

is incomplete (5–10%).

2- Cephalosporins may cause *pain at intramuscular* injection sites and *phlebitis* after I.V administration.

They may *increase the nephrotoxicity* of aminoglycosides when the two are administered together.

OTHER BETA-LACTAM DRUGS:

A. Aztreonam

- **Aztreonam is a monobactam that is resistant to beta-lactamases produced by certain gram-negative rods, including Klebsiella, Pseudomonas, and Serratia. *The drug has no activity against gram positive bacteria or anaerobes*.**
- **Aztreonam is administered intravenously and is eliminated via renal tubular secretion. Its half-life is prolonged in renal failure.**
- ***Adverse effects include* gastrointestinal upset with possible superinfection, vertigo and headache, and rarely hepatotoxicity.**

B. Imipenem, Doripenem, Meropenem, and Ertapenem:

- These drugs are carbapenems (chemically different from penicillins but retaining the beta-lactam ring structure)
- They have wide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes.
- *For pseudomonal infections*, they are often used in combination with an aminoglycoside.
- MRSA strains of staphylococci are resistant.

- **Imipenem is rapidly inactivated by *renal dehydropeptidase*-I and is administered in fixed combination with cilastatin, an inhibitor of this enzyme. Cilastatin increases the plasma half life of imipenem and inhibits the formation of potentially nephrotoxic metabolite.**
- **Adverse effects of imipenem-cilastatin include *gastrointestinal distress, skin rash*, and, at very high plasma levels, CNS toxicity (confusion, encephalopathy, seizures).**
- ***There is partial cross allergenicity with the penicillins.***

C. Beta-Lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam are used in fixed combinations with certain hydrolyzable penicillins.

- **They are most active against plasmid-encoded beta-lactamases such as those produced**

by *gonococci, streptococci, E coli*, and *H influenzae*.

- **They are not good inhibitors of inducible chromosomal beta-lactamases**

formed by *Enterobacter, Pseudomonas, and Serratia.*

OTHER CELL WALL OR MEMBRANE-ACTIVE AGENTS:

A. Vancomycin

- **Vancomycin is a bactericidal glycoprotein that binds to the *d-Ala-d-Ala* terminal of the nascent peptidoglycan pentapeptide side chain and *inhibits transglycosylation*. This action prevents elongation of the peptidoglycan chain and interferes with crosslinking.**
- **Resistance in strains of enterocci (vancomycin-resistant enterococci [VRE]) and staphylococci (vancomycin-resistant S aureus [VRSA]) involves a decreased affinity of vancomycin for the binding site**

Vancomycin has a narrow spectrum of activity and is *used for serious infections caused by drug-resistant gram-positive* organisms, including methicillin-resistant staphylococci (MRSA) and in combination with ceftriaxone for treatment of (PRSP). Vancomycin is for treatment of infections caused by *Clostridium difficile*.

- **Toxic effects of vancomycin include chills, fever, phlebitis, ototoxicity, and nephrotoxicity. Rapid intravenous infusion may cause diffuse flushing ("red man syndrome") from histamine release.**

B. Fosfomycin

Fosfomycin is an *antimetabolite inhibitor of cytosolic enolpyruvate transferase*. This action prevents the formation of N-acetylmuramic acid, an essential precursor molecule for peptidoglycan chain formation.

Fosfomycin is *excreted by the kidney*, with urinary *levels exceeding the minimal inhibitory concentrations* (MICs) for many urinary tract pathogens.

C. Bacitracin

Bacitracin is a peptide antibiotic that interferes with a late stage in cell wall synthesis in gram-positive organisms.

Because of its marked nephrotoxicity, the drug is limited to topical use.

E. Daptomycin

Daptomycin is a novel cyclic lipopeptide with spectrum similar to vancomycin but active against vancomycin-resistant strains of enterococci and staphylococci.

The drug is eliminated via the kidney. Creatine phosphokinase should be monitored since daptomycin may cause myopathy.